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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,337	BENOIT ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks mailed April 6, 2004.

Claims 1-39 are pending in the instant application. Claims 1 and 4 have been amended. Claims 34-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on October 20, 2003.

Claims 1-33, 38 and 39 have been on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

In the previous Office Action mailed November 28, 2003, the abstract of the disclosure was objected to because it comprised three paragraphs. An abstract should contain only a single paragraph. See MPEP § 608.01(b). **This objection is withdrawn** in view of Applicants Amendment to the Specification to limit the abstract o one paragraph.

Oath/Declaration

In the previous Office Action mailed November 28, 2003, the oath or declaration was found to be defective because the fourth inventor made non-initialed and/or non-dated alterations to the oath or declaration. See 37 CFR 1.52(c). A new oath or declaration in compliance with 37

CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. **This objection is withdrawn** in view of Applicants Amendment to provide a supplemental Oath/Declaration.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed November 28, 2003, claims 1, 2, and 4 were rejected under 35 U.S.C. 102(a) as being anticipated by Aihara et al. [GenBank Accession Number AF131884, Database DDBJ, submitted February 15, 2000].

It is noted that the limitations "a polynucleotide comprising a fragment of SEQ ID NO:1" and "a polynucleotide comprising a fragment of SEQ ID NO:2" of claims 1 and 4, respectively are given their broadest reasonable interpretations since the term "fragment" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree of the term "fragment". Therefore, the limitations "a polynucleotide comprising a fragment of SEQ ID NO:1" and "a polynucleotide comprising a fragment of SEQ ID NO:2" have been broadly interpreted as any polynucleotide comprising at least a 2 bp fragment of SEQ ID NO:1 or any polynucleotide comprising at least a 2 bp fragment of SEQ ID NO:2.

Aihara et al. disclose a 2074 bp sequence fragment of the human CVARP 5'-flanking region. **This rejection is withdrawn against claim 4, but maintained against claims 1 and 2** for the following reasons: This rejection is withdrawn against claim 4 in view of Applicants arguments. The Examiner has found persuasive Applicants argument that Aihara et al. disclose the identical sequence of SEQ ID NO:2, which is primarily the 5'-flanking region of the human CARP gene, and by definition, the identical sequence cannot be a fragment, and therefore Aihara

et al. does not anticipate SEQ ID NO:2. This rejection is maintained against claims 1 and 2 in view of the Examiner's reevaluation of the broadness of the claims to interpret the term "fragment" as comprising a polynucleotide comprising >20 bp fragment of SEQ ID NO:1. Aihara et al. still reads as art on the instant claims because Aihara et al. disclose a polynucleotide comprising a 30 bp fragment of SEQ ID NO:1 (see attached sequence alignment at Qy nucleobases 2135-2165).

Response to Arguments

In response to this rejection, Applicants argue that Aihara et al. disclose the identical sequence of SEQ ID NO:2, which is primarily the 5'-flanking region of the human CARP gene. Applicants argue that the claims recite a "fragment" and by definition, the identical sequence cannot be a fragment. Applicants further contend that the Examiner's interpretation of the term "fragment" is not reasonable because the claims recite a polynucleotide that induces expression in cardiac cell *in vivo* of a gene which is operably linked to said polynucleotide. Applicants also argue that one skilled in the art would have no basis for concluding that a polynucleotide comprising a 2 bp fragment of SEQ ID NO:1 or SEQ ID NO:2 would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide.

Applicant's arguments have been fully considered, and are found persuasive in part. The claims are broadly drawn to a polynucleotide comprising a fragment of SEQ ID NO:1. The term "fragment" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree of the term "fragment". Since Applicants have not disclosed what the term "fragment" is intended to encompass, the term is given its broadest reasonable

interpretation. Applicants argue that the broadest reasonable interpretation of a polynucleotide comprising a 2 bp fragment of SEQ ID NO:1 or SEQ ID NO:2 is not a reasonable interpretation because one skilled in the art would have no basis for concluding that a polynucleotide comprising a 2 bp fragment of SEQ ID NO:1 or SEQ ID NO:2 would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide. This has been found persuasive. The Examiner agrees that one skilled in the art would have no basis for concluding that a polynucleotide comprising a 2 bp fragment of SEQ ID NO:1 or SEQ ID NO:2 would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide. However, after reevaluating the broadness of the claims, the Examiner believes that one skilled in the art would have basis for concluding that a polynucleotide comprising a >20 bp fragment of SEQ ID NO:1 or SEQ ID NO:2 would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide, for example. Given this assertion, the polynucleotide disclosed by Aihara et al. still reads as art on the instant claims because Aihara et al. disclose a polynucleotide comprising a 30 bp fragment of SEQ ID NO:1 (see attached sequence alignment at Qy nucleobases 2135-2165). Therefore, Aihara et al. anticipate claims 1 and 2. Applicants also argue that Aihara et al. disclose the identical sequence of SEQ ID NO:2, which is primarily the 5'-flanking region of the human CARP gene, and by definition, the identical sequence cannot be a fragment. This is found persuasive and the rejection is withdrawn against claim 4 in this regard.

In summary, since the term "fragment" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree of the term "fragment", the term is given a broad interpretation of a polynucleotide comprising a >20 bp fragment of SEQ ID

NO:1, since one of skill in the art would reasonably conclude that a >20 bp polynucleotide fragment would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide. Aihara et al. anticipate the instant claims because they disclose a polynucleotide comprising a 30 bp fragment of SEQ ID NO:1. Aihara et al. do not disclose that the polynucleotide induces expression in cardiac cell *in vivo* of a gene which is operably linked to said polynucleotide, however, the polynucleotide disclosed by Aihara et al. meets all the structural limitations of the claims, and therefore is considered to possess the functional limitations of the claim, namely to ability to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide. Therefore, Aihara et al. anticipate claims 1, 2, and 4.

In the previous Office Action mailed November 28, 2003, claims 1-7, 20-27, 30, 31, 32, 33, 38, and 39 were rejected under 35 U.S.C. 102(b) as being anticipated by Kuo et al. (Development, 1999 Vol. 126:4223-4234).

Kuo et al. disclose the cloning of a 10 Kb fragment of the mouse CARP gene and the sequencing of a 2.5 Kb fragment upstream of the coding sequence. Kuo et al. further disclose the identification of 5' *cis* regulatory elements that control the cardiac specificity of the CARP gene by the design of luciferase reporter constructs whose expression were driven by 5' nested deletions of the mouse CARP promoter in the pXP2 plasmid (see Figure 3A). Kuo et al. further disclose deletions from the 5'-end of the fragment were made and showed that a region of 213 bp of the promoter between nucleotides –166 and +47, relative to the transcription start position +1, was sufficient to confer cardiospecific expression *in vitro*, which suggested the presence, at the 5'-end, of an element for controlling the specificity of the promoter (see Figure 3C). Kuo et al.

also generated transgenic mouse lines comprising a fragment of 2.5 Kb upstream of the CARP gene, showing specific expression of a transgene in cardiac and skeletal muscle cells at an early stage of embryonic development, this expression then being inhibited during development (see Figure 6). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed on November 28, 2003.

Response to Arguments

In response to this rejection, Applicants argue that Kuo et al. do not disclose the identical polynucleotide of the claimed invention. Applicants argue that Kuo et al. describe the ability of portions of the 5'-flanking region of the mouse CARP gene to regulate expression of reporter genes *in vitro* in cultured cardiomyocytes versus COS1 cells. Applicants assert that Kuo et al. only report the ability of such sequences to regulate region-specific expression of beta-galactosidase in the hearts of transgenic mice. Applicants assert that Kuo et al. fail to disclose that the CARP gene sequences only induce reporter gene expression in cardiac tissues *in vitro* or *in vivo*. Applicants argue that Kuo et al. do not anticipate the instant claims because they fail to disclose the identical polynucleotide fragments of the instant invention and do not teach every element of the claims.

Applicant's arguments have been fully considered, but are not found persuasive because the claims are broadly drawn to a polynucleotide comprising a fragment of SEQ ID NO:1 or SEQ ID NO:2. Nowhere do the claims require an identical polynucleotide of SEQ ID NO:1 or SEQ ID NO:2. Applicants have not disclosed what the term "fragment" is intended to encompass, therefore the Examiner has determined that one skilled in the art would reasonably

conclude that a polynucleotide comprising a >20 bp fragment of SEQ ID NO:1 or SEQ ID NO:2 would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide. Kuo et al. disclose deletions from the 5'-end of the fragment were made and showed that a region of 213 bp of the promoter between nucleotides –166 and +47, relative to the transcription start position +1, was sufficient to confer cardiospecific expression *in vitro*. The disclosure of Kuo et al. meets all the structural limitations of the claims, and therefore is considered to possess the functional limitations of the claim, namely to ability to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide. Therefore, Kuo et al. anticipate claims 1-7, 20-27, 30, 31, 32, 33, 38, and 39.

In the previous Office Action mailed November 28, 2003, claims 1-7, 20-25, 28, 29, 30, 31, 32, and 33 were rejected under 35 U.S.C. 102(e) as being anticipated by Chien et al. [WO 00/15821].

Chien et al. disclose a portion 5' of the coding sequence of the mouse CARP gene, situated between nucleotides –2285 and +62, relative to the transcription start position +1. This sequence was evaluated in particular for its *in vivo* activity in adenoviral vectors (see Abstract and SEQ ID NOs. 1 and 2). The levels of activity obtained remain very low, however, such that it was found to be necessary, in order to detect an activity *in vivo*, to isolate the promoter sequence between two inverted terminal repeats of an adeno-associated virus (AAV-ITR) (see Figures 1 and Example 2). **This rejection is withdrawn** in view of Applicants amendment to the claims to recite, "in the absence of inverted terminal repeat sequences from human adeno-associated virus", as Chien et al. disclose recombinant adenovirus vector comprising a fragment

of the CARP promoter in association with the inverted terminal repeat sequences from human adeno-associated virus.

In the previous Office Action mailed November 28, 2003, claims 1-5, 8, 9, and 12-15 were rejected under 35 U.S.C. 102(b) as being anticipated by Phillip et al. (Clinical Cancer Research, 1996 Vol. 2:59-68).

Phillip et al. disclose gene modification of primary tumor cells for active immunotherapy of human breast and ovarian cancer. Phillip et al. further disclose the design of two plasmid constructs pMP1IL2 and pMP6IL2, expressing IL-2 (see Figure 1). Phillip et al. further disclose the transfection of pMP1IL2 and pMP6IL2 in MCF7 breast cancer cells increased IL-2 gene expression (see Figures 3 and 4). **This rejection is withdrawn** in view of the Examiner's reevaluation of the broadness of the claims to interpret the term polynucleotide "fragment" with respect to the ability to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide, as recited in the instant claims, as a polynucleotide comprising a >20 bp fragment of SEQ ID NO:1 or SEQ ID NO:2, which would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide.

In the previous Office Action mailed November 28, 2003, claims 1-5, 10, 11, and 12 were rejected under 35 U.S.C. 102(b) as being anticipated by Alarco et al. (Journal of Bacteriology, 1999 Vol. 181:700-708).

Alarco et al. disclose the bZip transcription factor Cap1p is involved in multidrug resistance and oxidative stress response in *Candida albicans*. Alarco et al. further disclose the

expression of Cap1p in CJD21 cells transformed with plasmid pMK22 carrying the full-length Cap1 gene or a hyperactive allele of Cap1 (see Figure 2). **This rejection is withdrawn** in view of the Examiner's reevaluation of the broadness of the claims to interpret the term polynucleotide "fragment" with respect to the ability to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide, as recited in the instant claims, as a polynucleotide comprising a >20 bp fragment of SEQ ID NO:1 or SEQ ID NO:2, which would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide.

In the previous Office Action mailed November 28, 2003, claims 1-5, 16, and 17 were rejected under 35 U.S.C. 102(b) as being anticipated by Mohuczy et al. (Hypertension, 1999 Vol. 33:354-359).

Mohuczy et al. disclose the antisense inhibition of AT_1 receptor in vascular smooth muscle cells using adeno-associated virus (AAC) based vector. Mohuczy et al. further disclose the inhibition of AT_1 receptor expression in vascular smooth muscle cells following transfection of an AAC vector containing AT_1 receptor cDNA in the antisense orientation. **This rejection is withdrawn** in view of the Examiner's reevaluation of the broadness of the claims to interpret the term polynucleotide "fragment" with respect to the ability to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide, as recited in the instant claims, as a polynucleotide comprising a >20 bp fragment of SEQ ID NO:1 or SEQ ID NO:2, which would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide.

In the previous Office Action mailed November 28, 2003, claims 1-5, 18, and 19 were rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Circulation Research, 1998 Vol. 82:862-870).

Chen et al. disclose the overexpression of human endothelial nitric oxide synthase in rat vascular smooth muscle cells and in balloon-injured carotid artery (see Abstract). Chen et al. further disclose the design of a human endothelial nitric oxide synthase viral vector by inserting human endothelial nitric oxide synthase into the *Eco*RI site of the parental retroviral vector LXSN (see page 863, first column). **This rejection is withdrawn** in view of the Examiner's reevaluation of the broadness of the claims to interpret the term polynucleotide "fragment" with respect to the ability to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide, as recited in the instant claims, as a polynucleotide comprising a >20 bp fragment of SEQ ID NO:1 or SEQ ID NO:2, which would be able to induce cardiac-specific expression *in vivo* of genes operably linked to the polynucleotide.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

Claims 1, 2, 3, 6, 8, 10, 12, 13, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 38 are drawn to a polynucleotide comprising a fragment of SEQ ID NO:1, or a fragment of a sequence that hybridizes under high stringency conditions with SEQ ID NO:1, wherein said polynucleotide in the absence of inverted terminal repeat sequences from human adeno-associated virus specifically induces expression in cardiac cells *in vivo* of a gene which is operably linked to said polynucleotide. Claims 4, 5, 7, 9, 11, 14, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 39 are drawn to a polynucleotide comprising a fragment of SEQ ID NO:2 or a fragment having at least 80% sequence identity to a fragment of SEQ ID NO:2, wherein said polynucleotide in the absence of inverted terminal repeat sequences from human adeno-associated virus specifically induces expression in cardiac cells *in vivo* of a gene which is operably linked to said polynucleotide.

The instant invention specification teaches the expression of luciferase in cardiac cells following the injection of an adenoviral vector containing a polynucleotide sequence upstream of the CARP gene (see Figure 8, for example). Applicants Remarks, mailed April 6, 2004 at page 1, first paragraph discloses that "the specification (including Example 10) clearly indicates that the instant invention does not require inverted terminal repeat sequences from human adeno-

associated virus to achieve *in vivo* cardiac-specific expression of a gene." However, it is unclear whether the instant invention does not contain inverted terminal repeat sequences because the instant specification at Example 7 -Construction of an Adenovirus-, discloses an adenovirus allowing the expression of the luciferase under the control of the CARP promoter was constructed according to the method of Crouzet et al., the expression cassette being identical to that of the plasmid pXL3634. The specification goes on to teach that "a shuttle vector allowing recombination in *E. Coli* was constructed in two stages. First, the CARP promoter was introduced into the pXL3474 between the regions ITR- and pIX in order to generate the plasmid pXL3758. Plasmid pXL3759 was then generated by introducing into pXL3758, the fragment containing the luciferase cDNA and the SV40 polyadenylation site. pXL3759 is represented in Figure 6A." Referring to Figure 6A, pXL3759 clearly contains inverted terminal repeat sequences (see ITR-Ψ (1-385)). Therefore, it is unclear whether the specification (including Example 10) clearly teaches that the instant invention, does not require inverted terminal repeat sequences from human adeno-associated virus to achieve *in vivo* cardiac-specific expression of a gene, since pXL3759, in Figure 6, clearly contains inverted terminal repeat sequences (ITRs).

Chien et al. [WO 00/15821] teach that the CARP promoter in cooperation with the inverted terminal repeat (ITR) sequences from human adeno-associated virus (AAV) are effective in achieving cardiac tissue-specific transcription of transgenes both *in vitro* and *in vivo* (see page 4, lines 18-24). Chien et al. further teach the inclusion of both AAV-ITR sequences in the context of a cardiac-restricted recombinant adenovirus vector preserves the tissue-specificity of the cellular promoter activity *in vitro* and *in vivo* (see page 13, lines 25-28). In fact, Chien et al. teach that the CARP promoter without AAV-ITR does not exhibit transgene expression (see

Figure 2) and therefore, inclusion of AAV-ITR provides a general strategy to achieve tissue-specific transcription using other cellular promoters (see page 15, lines 1 and 2). Chien et al. conclude that the inclusion of the ITR sequences from AAV allows for cardiac tissue specific expression. Fu et al. (Nature Biotechnology, 1998 Vol. 16:253-257) show that the inclusion of both the left and right end segments of the AAV-ITR sequences imparts the ability to enhance the level as well as tissue specificity of the transgene expression using viral gene promoters or tissue-specific cellular gene promoters (see Abstract).

It is unclear whether the Specification present any examples wherein the CARP promoter without the cooperation of inverted terminal repeat (ITR) sequences from human adeno-associated virus (AAV) are effective in achieving cardiac tissue-specific transcription of transgenes *in vivo*.

The Art clearly teaches that the inclusion of AAV-ITR sequences preserves cardiac tissue-specificity (see Fu et al.). In fact the Art teaches that teach that the CARP promoter without AAV-ITR does not exhibit transgene expression (see Chien et al.). Taken together, these results suggest that the inclusion of AAV-ITR sequences from human adeno-associated virus to are required to achieve *in vivo* cardiac-specific expression of a gene. Given this art-recognized requirement and Applicants assertion that the instant invention does not require inverted terminal repeat sequences form human adeno-associated virus to achieve *in vivo* cardiac-specific expression of a gene, it would appear that at the time the invention was made, using the polynucleotide sequence upstream of the CARP gene as a promoter to induce expression of a transgene in cardiac cells *in vivo* is unpredictable.

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, as broadly claimed. Applicants Remarks mailed April 6, 2004, discloses that the specification (including Example 10) indicates that the instant invention does not require inverted terminal repeat sequences from human adeno-associated virus to achieve *in vivo* cardiac-specific expression of a gene. However, it is unclear whether the instant invention does not contain inverted terminal repeat sequences because Example 7 teaches the construction of pXL3759 and Figure 6 teaches pXL3759 clearly contains inverted terminal repeat sequences. The Art teaches that the inclusion of AAV-ITR sequences preserves cardiac tissue-specificity and is required for transgene expression.

The specification does not appear to provide specific guidance by which one skilled in the art would expect to be able to induce gene expression in cardiac cells *in vivo* using the CARP promoter without the cooperation of AAV-ITR. In order to practice the invention claimed one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include determining how to induce gene expression in cardiac cells *in vivo* using the CARP promoter without the cooperation of AAV-ITR, where the Art clearly teaches that AAV-ITR is required. Given the art recognized unpredictability, this determination would not be routine and would require undue trial and error experimentation.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor, the lack of working examples, and the quantity of experimentation that would be required, it would

require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is mailed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
June 23, 2004